Postoperative Follow-Up of Patients with Early Breast Cancer: Reappraisal of Serum Tumor Markers

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Abstract The purpose of this study was to determine the most appropriate tests and procedures to detect disease progression effectively during the postoperative follow-up of patients with early breast cancer. We reevaluated our current surveillance protocol which involves the intensive follow-up of 643 patients with stage I disease. With the exception of one case of bone metastasis, all cases of recurrence (97%) were suspected from abnormal results detected during surveillance involving physical examination, serial determination of tumor markers, and chest roentgenography. Among 15 patients with asymptomatic distant metastasis, disease recurrence was suspected in 12 (80%) because of increased levels of serum tumor markers. No disease recurrence was detected by routine complete blood counts or automated chemistry studies alone. Our experience indicates that an effective follow-up regimen for patients with early breast cancer may include careful history-taking, physical examination, and the determination of serum tumor markers every 3–6 months for the first 3 years, then less frequently thereafter, and chest roentgenography every 6 months for 5 years, in addition to annual mammography. Serial determination of the tumor markers tumor polypeptide antigen, NCC-ST-439, and either carcinoembryonic antigen or carbohydrate antigen 15-3, seems to be of value for the selection of patients who should undergo radiologic exploration. The health benefits and cost-effectiveness of a follow-up focused on the measurement of serum tumor markers need to be evaluated in large prospective randomized trials.

Key words Tumor polypeptide antigen · NCC-ST-439 · Cost effectiveness · Bone metastasis · Asymptomatic

Introduction

After primary treatment for breast cancer, patients remain under surveillance; however, the postoperative surveillance programs vary from center to center, and debate continues about the optimal frequency and necessary components of follow-up care. The most intensive follow-up regimens include frequent laboratory tests and routine imaging studies such as chest radiographs, bone scans, and ultrasonography of the liver for asymptomatic patients. Some researchers1,2 advocate an intensive follow-up strategy based on the concept that early detection of recurrence leads to disease control and extended survival, whereas others3 support a minimalistic policy of clinical follow-up limited to history and physical examination. Two large prospective randomized trials4,5 to evaluate the effectiveness of intensive follow-up have failed to show a significant survival advantage of intensive over minimalistic clinical follow-up. In fact, the American Society of Clinical Oncology has published guidelines6 for breast cancer surveillance that support a minimalistic protocol. The routine use of costly tests, including bone scan, for the surveillance of breast cancer may lack cost-effectiveness, particularly for patients with a low risk of distant metastasis. Thus, we reevaluated our current surveillance protocol, which involves intensive follow-up, to determine which tests and procedures should be carried out to detect disease progression effectively during postoperative follow-up for patients with early breast cancer.

Patients and Methods

At Kitakyushu Municipal Medical Center, a referral center in Fukuoka, Japan, we researched the tumor registry to identify patients with invasive breast cancer who had received initial treatment between January
1983 and December 1998. Excluding patients with both metachronous and synchronous cancer in the contralateral breast, 643 patients were identified with a diagnosis of stage I breast cancer, defined as tumors less than or equal to 2 cm and with negative axillary nodes. Although the patient population was registered in a prospective database, we performed a retrospective review of 33 patients with recurrence. In this review we analyzed the methods of detection and the levels of tumor markers.

The intensive surveillance of patients who have undergone initial treatment for invasive breast cancer included the collection of data on the history of symptoms, physical examinations, complete blood counts, automated chemistry studies including liver function tests, and the determination of serum tumor marker levels every 3–6 months for the first 3 years after primary therapy, every 6–12 months for the next 2 years, and annually thereafter. Chest roentgenography, ultrasound of the liver, and ultrasound of the ipsilateral conserved breast were done every 6 months for 5 years, then annually. Bone scans, mammography, and pelvic examinations were performed annually. All patients were encouraged to report new symptoms promptly. When disease recurrence was suspected from symptoms, physical examination, continued elevation of tumor markers, or other tests, then radiologic tests, including bone scintigraphy, computed tomography (CT) scan, and magnetic resonance imaging, were performed to confirm the recurrence.

Early-morning fasting blood samples were collected and centrifuged according to standard protocol. The sera were frozen and assayed within 1 week. The serum concentration of carcinoembryonic antigen (CEA) was determined by a radioimmunoassay using CEA RIA Bicent (Dainabot, Chiba, Japan) until February 1989, after which an enzyme immunoassay using the CEA Dainapack (Dainabot, Chiba, Japan) was done. The assays for carbohydrate antigen (CA) 15-3 were done using the Centocor CA15-3 RIA kit8,9 (Centocor, Malvern, PA, USA). The level of tissue polypeptide antigen (TPA)10 was determined by a radioimmunoassay using the Prolifigen TPA kit “Daichi” II (Daichi Isotope, Tokyo, Japan) until November 1996, after which an immunoradiometric assay using the Prolifigen TPA-M “Daichi”II11 (Daichi Isotope) was done. The level of the tumor marker NCC-ST-439 was measured using an enzyme immunoassay kit12 (Nippon Kayaku, Tokyo, Japan). The reagent was a monoclonal antibody that reacts with the tumor-related carbohydrate antigen, ST-439.13 The BCA225 level was determined with an enzyme immunoassay using the K Assay BCA225 kit14 (MBL, Nagoya, Japan). BCA225 is a glycoprotein identified in human breast carcinoma cells, that shows a restricted distribution in other human tissues.15 The upper limits of normality for these markers in healthy women without breast cancer, established by other investigators, are 5.0 ng/ml (2.5 ng/ml before February 1989) for CEA, 28.0 U/ml for CA15-3, 70.0 U/l (100.0 U/l before November 1996) for TPA, 7.0 U/ml for NCC-ST-439, and 160.0 U/ml for BCA225.

The sensitivity of a test was defined as the percentage of true-positive (TP) values in patients with asymptomatic disease recurrence: TP/(TP + FN) × 100, where FN = false negative. The specificity was defined as the percentage of true-negative (TN) values in patients without disease recurrence: TN/(TN + FP) × 100, where FP = false positive. A case of FP markers was defined when there was no evidence of recurrence over an 18-month surveillance period on various repeated radiologic tests including bone scan and CT scan. Total accuracy was calculated by: [(TN + TP)/(TN + TP + FP + FN)] × 100. The positive and negative predictive values were calculated by: TP/(TP + FP) × 100 and TN/(TN + FN) × 100, respectively. Patients with symptomatic disease recurrence were excluded from the analysis.

Results

During the study period, disease progression was diagnosed in 33 of the 643 patients with stage I breast cancer. The median follow-up period was 81 months (range 15–186 months). Local recurrences developed in eight patients, as ipsilateral breast tumors after breast-conserving therapy in three. Of the 25 patients with distant metastasis, 13 were found to have metastatic bone disease with at least one lytic bone lesion, 6 were found to have lung metastasis, and 4 were found to have disease recurrence in the neck or the parasternal or para-aortic lymph nodes. Brain metastasis was found in one patient and metastatic disease involving the liver and lung was found in another. Disease recurrence developed within 3 years of the initial treatment in 21 (64%) patients, and within 5 years of treatment in 28 (85%) patients (Table 1).

All local recurrences were detected by physical examination (Table 2). Two (25%) of the eight patients with local recurrence were found to have an elevated serum concentration of at least one of the five tumor markers. Disease progression was suspected from subjective symptoms or the findings of physical examinations in 10 (40%) of the 25 patients with distant metastases, and disease recurrence was confirmed by subsequent radiologic tests. Of the five patients with symptomatic bone metastases, two suffered pathologic fractures, and four required radiation therapy to the bone. When asymptomatic disease progression was detected by abnormal results of both laboratory tests and concurrent imaging studies at a routine follow-up visit,